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break there was thought to be a result of aerosol transmission to patients and family members on an open ward from a patient with pneumonia and the protean manifestations of Lassa fever,¹ a disease that is fatal in up to half the patients in West Africa who have it. Aerosol transmission was not ruled out in another outbreak, in Liberia. Thus, the possibility that Lassa fever might spread to countries outside Africa initially caused great alarm. Several countries organized systems, equipment, and procedures to protect against aerosol transmission of the disease. Aerosols containing the virus proved infectious in animals, and small amounts of virus were found in throat swabs of patients. Person-to-person transmission outside of hospitals in Africa has not been documented,² however; most cases of transmission to humans are believed to be due principally to aerosolization of urine from chronically infected rodents.

Lassa fever is a serious disease in tropical West Africa, causing an estimated 300,000 infections and 5000 deaths annually. In one region where the disease is hyperendemic (eastern Sierra Leone), it accounts for more than one third of all deaths on the hospital medical wards. The incubation period (7 to 18 days) is sufficiently long to allow persons infected in remote areas to travel anywhere in the world. Imported cases, which to date have been reported from the United States, Canada, Europe, Israel, and Japan, may increase with the rise in air travel to and from West Africa. A careful travel history is vital to the recognition of such cases, since the clinical presentation is often highly variable and nonspecific. The disease begins gradually, with fever, headache, malaise, and arthralgias, and progresses over several days to a generalized toxic syndrome with pharyngitis (often severe and exudative), retrosternal pain, vomiting, abdominal tenderness, and signs of vascular instability and capillary leakage, including hypotension, conjunctival injection, minor bleeding from the gums, nose, or other sites, edema of the face and neck, proteinuria, and a rising hematocrit. In different stages of illness, Lassa fever may be confused with influenza, malaria, streptococcal pharyngitis, diphtheria, typhoid fever, or rickettsiosis. Severe cases worsen in the second week after onset, with the development of the adult respiratory distress syndrome, encephalopathy, and shock. Convalescence may be complicated by pericarditis, congestive heart failure, or sensorineural deafness.

New data gathered through dedicated efforts by the Centers for Disease Control (CDC) and the Ministry of Health of Sierra Leone, by laboratory scientists in a small number of maximal-containment laboratories in this country and Europe, and by medical and public health teams that have dealt with cases of both endemic and imported Lassa fever have shed light on the features of the disease, and this has tended to reduce the fear of the virus as a highly contagious pathogen. The concentration of virus in the blood of patients varies by at least three orders of magnitude; the virus

IMPORTED LASSA FEVER — REEXAMINING THE ALGORITHMS

TWENTY years ago the arenavirus Lassa fever virus was identified as the cause of three serial, nosocomial cases of hemorrhagic fever in nursing personnel at a mission hospital in Jos, Nigeria. A subsequent out-

is recoverable only sporadically from the throat and urine of patients. High levels of viremia and high aspartate aminotransferase concentrations are highly predictive of mortality.^{3,4} Intravenous treatment with high doses of the purine nucleoside analogue ribavirin is effective therapy for life-threatening Lassa fever, particularly if initiated before the seventh day of illness.⁴ There is also evidence that ribavirin has efficacy when given in lower doses by mouth, with a bioavailability of about 45 percent when administered by this route.⁵ Data from studies in monkeys show that ribavirin and plasma containing virus-neutralizing antibodies are more effective together than either alone as therapy in this model of uniformly fatal disease.⁶ Finally, specific experience in 20 patients with imported Lassa fever revealed no instance of secondary transmission to medical staff or to the more than 1000 persons who had various degrees of contact with the patients. Accordingly, the CDC recently modified its recommendations for the care of patients, the protection of health care workers, and the surveillance of contacts.⁷ Basically, these guidelines call for universal precautions similar to those used against the acquired immunodeficiency syndrome and hepatitis, and for 21-day surveillance of known contacts of patients. Thus, Lassa fever joins a select group of viral illnesses, including those caused by human retroviruses and hepatitis B and C, that are characterized by marked viremia and substantial hazard from direct exposure to blood but low potential for transmission by aerosol, respiratory droplets, or casual contact.

The report in this issue of the *Journal* by Holmes and colleagues of the CDC⁸ serves to reinforce this policy. A Nigerian-born U.S. engineer became infected during an emergency trip to Nigeria to attend the funeral of his mother, who had probably died of Lassa fever. He fell sick after returning to the Chicago area and made several visits to medical institutions during the ensuing two weeks; no travel history was obtained. Eight members of his family were exposed to him during this interval, before he was finally admitted to the hospital in extremis, with the highest concentration of virus and aspartate aminotransferase yet recorded for this disease. Yet, apparently no transmission of the virus occurred. Although the interval before serologic testing might be considered somewhat brief, viral infection was not detected after prophylactic ribavirin had been administered to the patient's family. Indeed, in this sense, ribavirin has yet to be assessed as prophylaxis for Lassa fever.

Although the algorithm offered by Holmes et al. has much to recommend it, we believe that further thought is warranted before it is applied as a matter of rigid doctrine in the treatment of contacts of patients who have imported Lassa fever. Contacts at high risk should be treated prophylactically, but contacts treated thus should be limited to those directly exposed to blood or body fluids by penetration of intact or broken dermis or by direct exposure of mucosal surfaces. Kissing, sexual contact, and contact with droplets

from the eyes, in addition to needle wounds or gross contamination of ungloved hands, would fulfill this criterion. Beyond that, we do not perceive any reliable distinction between medium-risk, low-risk, and "no-risk" contacts. Contacts should be asked to report any fever or acute symptoms occurring during a period of 21 days to a designated surveillance office. Taking the temperature twice daily is not mandatory and is likely to cause excessive concern among contacts. We also believe that a fever (temperature, $\geq 38.3^{\circ}\text{C}$) lasting as little as 24 hours during surveillance should not automatically trigger intravenous treatment with ribavirin. Careful elucidation of all relevant data, including possible testing of the blood for the viral antigen,⁹ should precede this decision because the record to date shows that in this situation, other causes of fever are much more likely than is Lassa virus infection.

Similarly, we have reservations about the doses proposed by Holmes et al. for prophylactic treatment of high-risk contacts. Although only the younger children treated had a reduction in erythrocyte mass of 10 percent or more,⁸ we note that the dose recommended by the authors represents a substantial increase from that recommended by the 1988 guidelines.⁷ Prepubertal children, in particular, might better be treated with a dose based on their weight or body-surface area, as opposed to a standardized dose. Individual uptake of oral ribavirin may vary considerably: two of three persons who were infected with human immunodeficiency virus but had normal hemograms at base line were unable to tolerate ribavirin treatment when given 2400 mg per day for 14 days,¹⁰ the dose that Holmes et al. suggest for adults. The high level of efficacy of oral ribavirin (1000 mg per day) in the treatment of clinical Lassa fever with a low degree of viremia⁴ suggests that such doses might provide excellent prophylaxis. Other concerns about high-dose prophylaxis include the extensive hemolysis that may occur in persons with Gilbert's disease and the unresolved issues of the carcinogenicity and testicular toxicity of ribavirin in animals, and, by implication, in humans. Whatever doses are selected, all persons receiving prophylaxis should be treated according to a protocol that calls for frequent monitoring of the complete blood count, drug blood level, aspartate aminotransferase concentration, and viral titer. In view of the long terminal half-life of this drug,⁵ parenteral loading may be advisable to assist in rapid attainment of desired blood and crucial (if poorly documented) tissue levels of the drug, especially if the interval between high-risk exposure and initial treatment is several days.

Studies of Lassa fever should continue to receive high priority in West Africa, where the transmission of endemic disease facilitates continuous acquisition of new knowledge. We also suggest that government agencies directly involved in research on the disease and in its control and regulation exchange information, coordinate efforts, and ensure that maximal information is gained during the care of future patients with imported Lassa fever and their contacts. The

CDC should store small amounts of ribavirin for emergency use, the U.S. Army Medical Research and Development Command should supply some of its virus-neutralizing immune globulin for Lassa fever, and the Food and Drug Administration should offer advice on protocols for what effectively comprise Phase I-Phase II studies. Although ribavirin has proved to be highly effective and acceptably safe for treatment of patients with Lassa fever, until we have more information from a larger, detailed data base, great care should be taken in using this drug in high doses as prophylaxis.

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